II. REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Claims 47, 48, 50, 52-54 and 56 and 59-67 were pending and examined in the outstanding Office Action. In this Amendment and Reply, claims 47, 48, 52, 61-63, 65 and 66 were amended. Claims 50, 54, 57, 60 and 67 are canceled without prejudice or disclaimer. New claims 68 to 70 have been added.

The amendments to the claims and the addition of new claims 68 to 70 do not raise an issue of new matter. Support for the amendments to claims 47, 48, 52, and 61-63 is found in the application papers on pages 6 to 10. The newly-added claims also are supported in the application within these pages. Claims 65 and 66 have been amended to correct grammatical errors. Entry of these amendments is respectfully requested. The amendments to the claims and the cancellation of other claims is not intended to be a dedication to the public of the subject matter of the claims as previously presented. Applicants reserves the right to file on or more claims to this subject matter in one or more related continuation applications.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 47, 48, 52, 53, 56, 61-66 and 68-70 are presently under examination.

In view of the previous amendments and the remarks which follow, reconsideration and withdrawal of the objections and rejections is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claim 67 was rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. The Office noted that this is a New Matter rejection. Without conceding the correctness of the Office's position and merely to advance examination of the application, claim 67 has been canceled without prejudice or disclaimer thereby obviating this ground for rejection.

Claims 47, 48, 50, 52-54, 56, 57 and 59-67 were rejected for allegedly failing to be enabled by the specification. The Office alleged that the specification does not enable screening any subject for sensitivity to any TS directed chemotherapeutic drug by genotyping the subject's 28 base pair repeat in the 5 'UTR of the TS gene. The claims were further rejected on the ground that only human tissue was genotyped while the claims are not so limited. Applicants respectfully traverse for the reasons which follow.

Claims 47, 48, 52, 53, and 61-66 have been amended to specifically recite that only human tissue is genotyped using the methods of the invention. Claims 50, 56 and 57 and 67 have been canceled without prejudice or disclaimer. Accordingly, this ground for rejection should now be removed.

Turning now to the objection that the specification does not enable the full breadth of the language "TS-directed chemotherapeutic drug" in the claims. In support of its position, the Office alleged that the application was not enabled for any TS-directed chemotherapeutic drug and relied on the alleged teaching in Papamicheal (1999) The Oncologist that not all TS-directed drugs are as active as 5-FU in treating colorectal cancers. Applicants traverse for the reasons which follow.

First, Applicants agree that the specification defines the term "TS-directed drug" as those that involve or are targeted against or are based on thymidylate synthase (TS). Prior to the effective filing date of the claims, TS was a well-characterized enzyme known to be over-expressed in certain cancers such as colorectal cancers. (See references (1) through (9) noted on page 16 of the application papers). The mechanism of action of TS-directed drugs such as 5-FU (a TS-inhibitor) was well known and alternatives with the same or similar mechanism of action

were tested and under clinical development. It is unclear if the Papamichael reference cited by the Office was actually published prior to the effective filing date of November 15, 1999 (the reference notes that the paper was only accepted for publication about one month prior on October 17, 1999) but it is a review paper and as such, it does summarize seventy-two (72) prior published scientific journal articles that describe 5-FU analogs and prodrugs with the same or similar mechanism of action as 5-FU.

Applicants' specification describes a class of TS-directed drugs, e.g., the fluoropyrimidines and notes 5-FU as a specific example of such drugs. Applicants submit that this disclosure, in light of the teachings of the specification, the claimed subject matter and the knowledge available to the skilled artisan at the time the invention was filed, fully enables the term "TS-directed chemotherapeutic drug" in the claims.

The pending claims are directed to screening a biological sample isolated from a human patient suffering from colorectal cancer for a 28 base pair repeat that may be present in the 5' UTR of the TS gene. If the patient is heterozygous or homozygous for a double repeat of the 28 base pair repeat, the patient is likely to respond to a TS-directed drug, such as a flouropyrimidine. As established by the Papamichael reference noted by the Office, prior to the effective filing date of the application, TS was a well known target for chemotherapeutics for the treatment of colorectal cancer. 5-FU was a well established chemotherapy for colorectal cancer and it was know to work by inhibiting the action of TS, an enzyme known to be over-expressed by colorectal cancer patients. Analogs and prodrugs of 5-FU, a TS-directed drug, were known to those of skill in the art prior to the effective filing date of the application.

Moreover, the variability in patient response noted by Papamichael is the art-recognized problem that the current invention solves. Even within the patient population reported by Applicants in the application papers, not all patients were considered responders to TS-directed chemotherapy. By screening colorectal patients prior to initiating any TS-directed drug therapy (or any other therapy for that matter), the clinician and patient can avoid treatments that are unlikely to produce a positive clinical outcome. As noted by the Office on page 6 of the Office

Action, Applicants' disclosure removes the necessity for the random search for polymorphisms that may be linked to a positive therapeutic outcome. In conclusion, with the teachings of Applicants' specification in hand, as well as the characterization of the TS enzyme and the knowledge of drugs with the same or similar mechanism of action to 5-FU, it would not require undue experimentation to use the claimed screen and method to identify patients that are likely to respond to TS-directed chemotherapeutic agents other than 5-FU.

In view of the preceding amendments and remarks, Applicants respectfully request that the Office reconsider and withdraw the ground for rejection of the claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, Second Paragraph

Claims 57-60, 61, 63 and 66-67 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office argued that the term "means for determining a genomic polymorphism" is vague because it can include a number of different functions such as amplifying, detecting sizes on a gel, etc. and it cannot be determined what specific function the "means" is drawn to.

Without conceding the correctness of the Office's position and merely to advance prosecution of the pending claims, claims 57 has been canceled without prejudice or disclaimer. All claims that depend from it have been canceled as well. Removal of the rejection is therefore respectfully requested.

Claim 61 was objected to for allegedly lacking antecedent basis for the term "biological sample fluid." The claim has been amended in a sincere effort to remove the grounds for objection. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 59 was objected to for use of the term "may be". Without conceding the correctness of the Office's position, the claim has been canceled without prejudice or

disclaimer thereby obviating the grounds for rejection.

Claim 67 was objected to for use of the term "cancer associated with disseminated colon cancer." Without conceding the correctness of the Office's position, the claim has been canceled without prejudice or disclaimer thereby obviating the grounds for rejection.

Accordingly, in view of the preceding amendments and remarks, reconsideration and withdrawal of the objections and rejections under 35 U.S.C. § 112, second paragraph are respectfully requested.

35 U.S.C. § 102

Claim 57 was rejected under 35 U.S.C. § 102(b) as allegedly anticipated by New England Biolabs Catalog (1996, page 102), for the reasons of record.

Claims 57-59 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Promega Catalog (19971, page 78 on the ground it teaches a kit comprising Taq DNA polymerase as a means for determining a genomic polymorphism at a tandemly repeated 28 base pair sequence.

Without conceding the correctness of the Office's position, claims 57-59 have been canceled without prejudice or disclaimer thereby obviating the grounds for rejection.

35 U.S.C. § 103

The Kit Claims

Claims 57 and 59-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie in view Erlich (US Patent 5,468,613) Baxter-Lowe (US Patent No. 5,702,885) and and New England Biolabs. The Office stated that Horie teaches a method for analyzing the number of repeats in the 5' UTR of the TS gene using PCR and size analysis on a gel (see page

192, col. 2-page 193; Figure 3). With regard to claims 57 and 59, the Office noted that the primers are considered means for determining a genomic polymorphism in the TS 5' UTR. The Office further argued that the first primer taught by Horie is identical to instant SEQ ID NO: 6, and the 2nd primer of Horie "comprises" instant SEQ ID NO: 7 (contains 9 additional nucleotides on the *5'* end), which are the primers the specification teaches were used to "determine" the presence of the TS polymorphism. With regard to claims 57 and 59, the Office argued that Horie teaches using Taq polymerase, dNTPs, and reaction buffer for the PCR reaction, and further teaches analysis on a 4% agarose gel, the use of molecular markers for size analysis, as well as DNA tandemly repeated sequences. The Office admitted that Horie does not teach packaging these means and reagents in kit format, but relied on Erlich to teach constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays and further that Erlich teaches providing kits which include reagents for identifying alleles in hybridization assay. The Office also argued that therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie, for determining the TS 5' UTR repeat alleles of a subject, in kit format, for the obvious improvement of providing the reagents in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The Office stated that the ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie more convenient to perform. The Office also stated that it would have been further obvious to provide either size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was co only used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. The Office further remarked that the use for the kit, the instructions in the kit and the temperature of the buffer solution carry no patentable weight as they does not provide any structural limitation to the kit.

With respect to claim 60, the Office argued that it would have been further obvious to

provide either size markers, or the sequences of the differently tandemly repeated alleles as positive controls in order to provide a comparison.

Without conceding the correctness of the Office's position and merely to advance the remaining claims to allowance, the claims directed to a kit have been canceled. Applicants reserve the right to file one or more continuation applications with the same or similar claims.

The Screen Claims

For the sake of brevity and conciseness, Applicants are re-stating up front all grounds for rejecting the claims as allegedly obvious over the cited art and summarizing the Office's position regarding the teachings of the references applied against these claims. Applicants' rebuttal to the Office's positions with respect to each reference as applied to the claims follows this summary and is intended to be applied to each ground of rejection raised by the Office. As noted above, the claims to a kit (claims 57-60) have been canceled without prejudice or disclaimer and therefore are not addressed below.

Claims 47-48, 52-54, 56, 64 and 67 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman in view of Ruano.

Claims 47-48, 50, 52-54, 56, 64 and 67 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman and Kawakami (Kawakami et al; Proc. Annu. Meet. Am. Soc. Clin. Oncol. Vol. 17, pp A1128, May 1998) in view of Ruano.

Claims 61-66 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

Claims 61-66 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman and Kawakami in view of Ruano, as applied to claims 47-48, 50, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

Applicants respectfully traverse for the reasons which follow. Two independent claims are pending and under consideration. Independent claim 47, as amended, and new claim 68 are directed to a method for screening a patient for sensitivity to a thymidylate synthase (TS) – directed chemotherapeutic drug by the steps of: 1) determining the genotype of the patient's biological sample at a tandemly repeated 28 base pair sequence in the 5' untranslated region (UTR) of a TS gene in the biological sample; 2) correlating said genotype to said sensitivity to TS – directed chemotherapy. Claims 48, 50, 52 – 54, 64, 67 depend on claim 47 and therefore incorporate by reference all the limitations of the independent base claim. New claims 69 and 70 depend on new independent claim 68 and therefore incorporate by reference all the limitations of claim 68.

Horie is alleged to teach that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column) and that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie also is alleged to teach detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). The Office stated that while Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). The Office admits that Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs; however, Leichman et al is alleged to disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman also is alleged to teach that expression levels of TS correlated with sensitivity to 5-FU in the subjects and that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could

be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Ruano is alleged to teach that genetic variability is a determinant of a patient's response to therapy and that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Ruano was further alleged to teach that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

The Office also stated that although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to TS directed chemotherapy drugs. The Office argued that the ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create a prognostic test for customizing therapy based on a patient's genotype. The Office further alleged that Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

The Office also argued that given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was

found to be polymorphic among individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

Kawakami et al. is newly cited and applied against the claims by the Office. The Office alleged that Kawakami et al. teaches investigating the association between the TS 5' UTR tandemly repeated sequence and expression of TS in cancers. The Office also cited the reference for teaching that TS expression correlated with the number of repeats and teaches a level of 1.07 for the 2R/2R genotype, 1.38 for the 2R/3R genotype, and 2.59 for the 3R1/3R genotype.

Howells is cited for teaching correlation of GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Govindarajan is cited for teaching a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan also is alleged to teach that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Applicants respectfully traverse. The criteria for evaluating an invention under 35 U.S.C. § 103 is recited in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). In this reported decision, the Supreme Court set forth various factual inquiries and so-called "secondary considerations" or indicia of non-obviousness. The Supreme Court stated:

> "Under 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs,

> failure of others, etc., might be utilized to give light to the circumstances (383 U.S. 1, 18) surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."

Using these criteria as a guide, Applicants have reviewed the cited art. The primary reference relied upon by the Office in rejecting all claims under 35 U.S.C. § 103 is Horie et al. (Cell Structure and Function (1995) 20:191-197, "Horie").

In comparing the scope and teaching of the cited references against the claims, Applicants respectfully submit that Horie does not teach as the Office has suggested because the data reported in Horie is derived from an artificial in vitro system linking polymorphic 5' UTR TS promoter to a reporter CAT gene. TS gene expression in a sample isolated from the patient was not measured. Thus, contrary to the Office's assertion, Applicants' submit that Horie does not teach that TS expression is associated with the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene because TS expression in a human patient sample was not measured in Horie's system. Support for this interpretation of the teachings of Horie is found in the last paragraph of the reference, which is copied below.

> "A difference in the actual number of specific repeated sequences is known to be related to certain inherited diseases. However, the polymorphism in the repeated sequences in the 5'-terminal region of the hTS gene was detected among normal human individuals and at present, there are no data to suggest that the polymorphism might be related to any abnormal physical condition. Taking into account the essential role of the TS enzyme in biological systems, we find it interesting that the DNA polymorphism in the hTS gene seemed to have no effect on the physical condition of the individuals from which the genes were isolated, although the expression of the reporter gene linked to the polymorphic region of the hTS gene with its promoter depended on the structure of the polymorphic region in the transient expression assay. <u>At present, it is not clear whether the polymorphism-related difference in the transient expression assay affects the biological systems that involve the TS enzyme.</u> Further studies are needed to clarify the effects of the variable number of repetitions in the unique structure of the hTS gene on biological systems."
>
> Emphasis added.

Applicants maintain their position that the Office has failed to support its prima facie case against all the claim because in utilizing the primary Horie reference, it has failed to consider all the teachings of Horie and therefore acknowledges the limitations the authors themselves placed on interpretation of the results reported in the reference. *See, In re Inland Steel*, 265 F3d 1354 (Fed. Cir. 2001) (prior art must be considered for all it teaches; one cannot pick and choose from the reference only what is need to support a given position to the exclusion of other parts necessary to appreciate what the reference suggests to one skilled in the art). For example, the Office relies on the Abstract of Horie wherein it states that the number of repeated sequences in the 5' UTR of the TS gene resulted in differences in expression activity of the gene (see the Office Action at page 15, lines 11 to 13; page 20, lines 11 to 16; page 24, lines 13 to 18 and incorporated by reference at page 27, lines 14 and 15). This statement (that the number of repeated sequences in the 5 'UTR of the TS gene resulted in differences in expression of the gene) is taken out of the complete context of the paper and does not give weight to the authors' statements regarding the limitations of the reported data. Horie reports the results of an artifical system – ***the authors measured the expression of a transiently transfected CAT reporter gene in an vitro system***. In the concluding paragraphs, Horie cautions that this reported data is not predictive of what may occur in a true biological system. Horie states on page 196, right hand column that:

> "A difference in the actual number of specific repeated sequences is known to be related to certain inherited diseases. However, the polymorphism in the repeated sequences in the 5'-terminal region of the hTS gene was detected among normal human individuals and at present, there are no data to suggest that the polymorphism might be related to any abnormal physical condition. Taking into account the essential role of the TS enzyme in biological systems, we find it interesting that the DNA polymorphism in the hTS gene seemed to have no effect on the physical condition of the individuals from which the genes were isolated, although the expression of the reporter gene linked to the polymorphic region of the hTS gene with its promoter depended on the structure of the polymorphic region in the transient expression assay. At present, it is not clear whether the polymorphism-related difference in the transient expression assay affects the biological systems that involve the TS enzyme. Further studies are needed to clarify the effects of the variable number of repetitions in the unique structure of the hTS gene on biological systems."

Thus, Horie does not teach as the Office suggests. The secondary references fail to overcome the deficiency present in the primary Horie reference. Stated another way, while Horie does teach that the 5' UTR is related to gene expression of a reporter CAT gene, expression of TS was not measured neither in a healthy patient nor in a cancer patient. Because expression of the TS gene in a patient sample was not measured, the claimed nexus (i.e., motivation to combine) between the teachings of Horie and Leichman is absent. Because Horie does not teach that the polymorphism in the 5 'UTR correlates to TS expression in a patient sample, one of skill in the art would not have been motivated to combine the references with any reasonable expectation of success.. The Office's position, at best, appears not to be based on the teachings of the references as whole, but to be based on the knowledge learned from the Applicants' disclosure which cannot support a finding of obviousness. *See In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."). The motivation to combine the references cannot come from the teachings of the specification itself. *In re Lee*, 277 F.3d 1338, 1343, *citing W.L. Gore v. Garlock, Inc.* 721 F.2d 1540, 1553 (Fed. Cir. 1983) (it is improper to use that which the inventor taught against its teacher). Evidence that the Office has supported the basis for the combination of Horie with the secondary references is found on page 21 of the Office Action which points to Applicants' specification for support to apply the Office's interpretation of Horie to the secondary references: "[Applicants'] specification states "Patients with triple repeat in the TS gene as expected from in vitro models had higher gene expression levels..." (emphasis in Office Action). This statement relates to the Applicants' own work and therefore it cannot be used against the Applicants as prior art or in framing a rejection under 35 U.S.C. § 103. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645 (Fed. Cir. 1984).

In further support of their position as to the teachings of the cited reference, Applicants also direct the Examiner to the declaration of Dr. Danenberg submitted to the Office in the reply filed July 27, 2006. Dr. Danenberg, as one of skill in the art, stated that the system employed and reported in Horie is very different from the system described by Applicants and does not

represent cells in the native environment in the body of a patient. The Office disregarded Dr. Danenberg's declaration on the ground that the statements were conclusory without providing any facts to support the assertions made therein. Applicants' submit that, as stated in MPEP § 716.01(c) III, that opinion rebuttal testimony should not be disregarded:

> "[a]lthough factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. ... (*In re Lindell*, 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate issue not evident in the case, "some weight ought to be given to a persuasive supported statement of one skilled in the on what was not obvious to him. 385 F.2d at 456, 155 USPQ at 524."

As noted previously on page 21, lines 13 to 18 of the Office Action, the Office asserted that the statements made in the Danenberg declaration appear to contradict statements appearing on page 10, lines 18 to 19 of the application papers. Applicants respectfully disagree because the statements made on page 10, lines 18 to 19 of the specification relate to the Applicants' own work. Accordingly, the declaration does not contradict the teachings of Applicants' specification.

On page 21, lines 2 to 8, the Office questioned the statements made in paragraph 6 of the Danenberg declaration, specifically:

> "6. The studies reported in Horie determined expression levels of the TS gene using the CAT reporter gene. The specification and pending claims are directed to the levels of mRNA expression isolated from patients and how these levels correlate to the polymorphisms."

Applicants traverse. Support for this statement in the Danenberg declaration can be found in page 11, lines 8 to 13 of the application papers wherein it recites:

> "Although, it has been known that TS mRNA levels are a determinant of response to fluoropyrmidine based chemotherapy and survival in patients with gastric and colorectal cancers (2,3), the significance of TS polymorphisms in determining TS expression has not been previously studied. The results of the examples herein establish that the polymorphism in the hTS gene affects the TS mRNA levels in tumors and in normal tissue."

With respect to the secondary Leichman reference, it fails to shore up the deficiencies present in the primary Horie reference. In comparing the scope and content of the teachings of Leichman, Applicants submit that the reference does not teach as broadly as opined by the Office. Applicants submit that Leichman teaches that overexpression of TS was found in some, but not all patient tumor samples. The authors note that the reported data has limitations. For example in the left hand column of page 3227, the authors state that data reports on an average ratio of the TS gene to a control (in this case, β-actin) and that the method used to determine TS levels has limitations that preclude exact assessment of intratumoral TS.

Kawakami et al. also does not teach as broadly suggested by the Office. This paper reports on TS protein content by a radioligand-binding assay using a covalent complex formed between TS and [^{3}H]FdUMP. The frequency of the 2R/2R genotype this group was noted in only two out of 68 patients studied (less than 5 %). A later publication authored by Dr. Danenberg, "Pharmacogenomics of Thymidylate Synthase in Cancer Treatment" Frontiers in Bioscience **9**:2484-2949 (2004), questions the conclusions made by the Kawakami et al. group noting that 2R/R genotype was too low to evaluate the correlation with TS content. Thus, Kawakami et al. did not correlate the polymorphism with TS content.

In sum, Applicants maintain that the Office has failed to present a prima facie case against all pending claims under 35 U.S.C. § 103, for the following reasons:

1. Applicants disagree with the Office's characterization of the teachings of the primary reference Horie, to one skilled in the art;

2. Applicants disagree with the Office's characterization of the teachings of the secondary reference Leichman, to one skilled in the art;

3. Applicants disagree with the Office's characterization of the teachings of the secondary reference Kawakami et al., to one skilled in the art

4. Applicants submit that in view of the above, the fundamental teachings of the references are absent;

5. Applicants disagree that the requisite motivation to combine the references is present in the references; and

6. the Office's statement of rejection under 35 U.S.C. § 103, is based on impermissible hindsight using Applicants' specification as a guide.

Accordingly, in view of the preceding amendments and remarks, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103.

Applicants also bring to the Office's attention a review paper authored by Dr. Danenberg. A copy of the article is attached to the Supplemental Information Disclosure Statement that is concurrently filed with this reply. While the paper is published well after the 1999 effective filing date, Applicants note that it summarizes the research to 2004 regarding TS genomic polymorphisms and their clinical application.

Obviousness-Type Double Patenting

Claims 47, 48, 50, 52-54, 56, 57, 59-60 and 67, were provisionally rejected on the ground of obviousness-type double patenting over claims 1 to 9 of co-pending application No. 10/522,664.

Claims 61-66 were provisionally rejected on the ground of obviousness-type double patenting over claims 1 to 9 of co-pending application No. 10/522,664, in view of Horie, Howells and Govindarajan.

Applicants respectfully defer responding to these grounds of rejection until allowable subject matter has been indicated in either of the allegedly conflicting applications.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: April 12, 2007

By 

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